

the immunoglobulin light chain, are withdrawn from consideration by the Examiner at this time. Thus, claims 23-27, 29-35, and 37-45 are pending for consideration before the office.

**Rejection Under 35 U.S.C. § 102**

Claims 23-27, 29-31, 35, 40-42, and 45 are rejected under 35 U.S.C. § 102(b) as being anticipated by Konig *et al.* (WO 96/25435).

The claims as they stand are directed to a method of inhibiting the formation of amyloid deposits, removing amyloid deposits, or modulating the formation of amyloid deposits in a patient comprising administering to the patient an immunoglobulin polypeptide or fragment thereof that binds to an amyloid fibril or component or precursor thereof. Konig *et al.* disclose methods of generating antibodies against the A $\beta$  peptide and methods of using the antibodies to detect amyloid plaques. The cited reference shows only the results of immunohistochemical studies performed with the antibodies. Specifically, Konig *et al.* show only use of the antibodies to stain amyloid plaques in a formic acid treated, paraffin embedded 10  $\mu$ m thick section from a postmortem brain. Konig *et al.* do not disclose administering the antibodies to a patient to inhibit or modulate the formation of amyloid deposits or to remove amyloid deposits. Accordingly, Konig *et al.* do not anticipate the claimed invention. Applicants respectfully request the withdrawal of the rejection.

**Rejection Under 35 U.S.C. § 103(a)**

Claims 23-27, 29-35, and 37-45 are rejected under 35 U.S. C. § 103(a) as being unpatentable over Walker *et al.*, Konig *et al.*, Becker *et al.* and Immunology: A Short Course (Benjamini & Leskowitz Ed.).

Walker *et al.* disclose a diagnostic method for detecting amyloid deposits comprising injecting monoclonal antibody 10D5 into the cerebrospinal fluid of the brain of a monkey and detecting amyloid deposits by performing postmortem immunohistochemistry on a para-formaldehyde fixed tissue section of the brain of a monkey. Walker *et al.* show that amyloid deposits in the monkey's brain were labeled by the antibody. However, Walker *et al.* do not teach a method of treatment comprising administering antibodies to a patient to inhibit or modulate formation of amyloid deposits or remove amyloid deposits.

Likewise, as discussed above, Konig *et al.* do not disclose a method of administering antibodies to a patient to inhibit or modulate the formation of amyloid deposits or to remove amyloid deposits from the patient. Konig *et al.* show that the Mab 369.2B antibody is a useful postmortem diagnostic agent for *in vitro* immunohistochemical studies. However, it is not predictable whether this antibody would have been effective in inhibiting and modulating the formation of amyloid deposits in a patient or removing amyloid deposits from a patient. As discussed in the attached declaration, the effectiveness of an antibody as an *ex vivo* or *in vitro* diagnostic tool does not suggest its effectiveness as an agent for inhibiting or modulating the formation of amyloid deposits in a patient or for removing amyloid deposits from a patient. Moreover, Mab 369.2B has not been tested for *in vivo* administration. It is not even predictable that Mab 369.2B would bind an amyloid deposit in an *in vivo* system. Thus, Konig *et al.* do not provide the missing elements of Walker *et al.* to render the claimed invention obvious.

Similarly, Becker *et al.* (Nettleship) do not teach a method of treatment comprising administering antibodies to a patient to inhibit or modulate the formation of amyloid deposits or to remove amyloid deposits. Although Becker *et al.* generally discuss using antibodies having a specificity for  $\beta$ -amyloid peptide for diagnostic and therapeutic purposes, they fail to disclose any examples of the use of such an antibody for therapeutic purposes. Rather, the main focus of the disclosure is the use of such an antibody in *in vitro* diagnostic screening assays for potential inhibitors of  $\beta$ -amyloid neurotoxicity. At the time of Applicants' invention, it was not predictable that such an antibody would be effective in inhibiting or modulating the formation of amyloid deposits in a patient or in removing amyloid deposits from a patient. Accordingly, Becker *et al.* do not contain the elements missing from Walker *et al.* and Konig *et al.* to render the claimed invention obvious.

Benjamini is cited because it provides a definition for "opsonization". However, none of the other three cited references suggest that the antibodies disclosed therein are acting as opsonins.

The claimed invention is directed to a method of inhibiting the formation of amyloid deposits, removing amyloid deposits, or modulating the formation of amyloid deposits in a patient comprising administering to the patient an immunoglobulin polypeptide or fragment

thereof that binds to an amyloid fibril or component or precursor thereof. Applicants unexpectedly showed that antibodies against amyloid fibrils are effective in removing amyloid deposits in a patient. Thus, Applicants unexpectedly discovered a method of treating a patient suffering from amyloid deposits comprising administering antibodies to the patient to inhibit the formation of amyloid deposits, to modulate the formation of amyloid deposits, and to remove amyloid deposits.

Attached is a declaration under 37 CFR § 1.132 by Dr. Anja Leona Biere, a scientist in the field of amyloidosis. The declaration sets forth the state of the art at the time of Applicants' invention and the reasons why Applicants' claimed method of using antibodies to treat patients suffering from amyloid deposits is not obvious in view of the cited references. The references cited in the declaration and in this response have been listed on a Form 1449 for the Examiner's convenience.

At the time of Applicants' invention, the only treatment available for patients with systemic amyloid-associated diseases involved attempting to reduce the synthesis of the amyloidogenic precursor protein, *e.g.*, in cases of primary (AL) amyloidosis, such therapy involved the use of anti-plasma cell chemotherapy given in conventional doses or high doses in combination with autologous stem cell transplantation (in rare instances, localized amyloid deposits such as in the larynx or bladder were removed surgically); for secondary (AA) amyloidosis, administration of anti-inflammatory agents (Falk *et al.*, *The New England Journal of Medicine*, 1997, 337 (13): 898-908; Schehr, R., *BioTechnology*, 1994, 12:140-144); for hereditary amyloidosis (ATTR), liver transplantation (Holmgren *et al.*, *Lancet*, 1993, 341:1113-1116). None of these approaches for treating patients with primary, secondary, or hereditary forms of amyloidosis renders the claimed method of treatment discovered by Applicants obvious. Further, prior to Applicants' invention, no treatment was available for removing amyloid deposits in other amyloid-associated systemic diseases, *e.g.*, type 2 diabetes, or in amyloid-associated brain disorders, *e.g.*, Alzheimer's disease.

In fact, at the time of Applicants' invention, the focus of the amyloidosis research was inhibiting formation of the precursor protein with agents other than antibodies (Kisilevsky R., *Drugs & Aging*, 1996; 8 (2):75-83). Scientists in the field of amyloidosis research at the time of Applicants' invention would not have considered the use of antibodies as a viable treatment

option because it was believed that amyloid deposits in patients were not recognized by the human body as foreign materials that would induce a humoral (antibody-based) immune response.

Further, as discussed in the declaration, though the use of antibodies as research tools and for diagnostic purposes was known to the skilled artisan at the time of Applicants' invention, it was not predictable that antibodies capable of binding and detecting amyloid deposits *in vitro* would have been effective in inhibiting and modulating the formation of amyloid deposits and in removing amyloid deposits from patients *in vivo*. The mere binding of an antibody to amyloid fibril for diagnostic purposes is not sufficiently predictive of its ability to inhibit or modulate formation of amyloid fibril or remove amyloid fibril from a patient.

Accordingly, due to the unpredictable nature of the invention and for the reasons discussed above, the combination of the cited references do not render the claimed invention obvious.

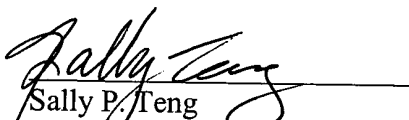
### CONCLUSION

In view of the accompanying remarks, Applicants respectfully request reconsideration and timely allowance of the pending claims. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact Applicants' undersigned representative to expedite prosecution.

If there is any fee due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

**MORGAN, LEWIS & BOCKIUS LLP**

  
Sally P. Teng  
Reg. No. 45,397

Dated: October 23, 2002

**Customer No. 009629**

**MORGAN, LEWIS & BOCKIUS LLP**

1111 Pennsylvania Ave., N.W.

Washington, D.C. 20004

(202) 739-3000